NIH RELAIS Document Delivery

NIH-10096750

NIH -- W1 JO828DR

PAMELA GEHRON ROBEY
CSDB/NIDR/NIH Bldng 30 Rm 228
30 CONVENT DRIVE MSC 4320
BETHESDA, MD 20892

ATTN:
PHONE: 301-496-4563
FAX: 301-402-0824
E-MAIL:

SUBMITTED: 2001-12-21 15:15:04
PRINTED: 2001-12-27 07:43:30
REQUEST NO.: NIH-10096750
SENT VIA: LOAN DOC
5363319

NIH Fiche to Paper Journal

TITLE:	JOURNAL OF PEDIATRIC ENDOCRINOLOGY _METABOLISM : JPEM
PUBLISHER/PLACE:	Freund Pub. House, London :
VOLUME/ISSUE/PAGES:	1998 Jul-Aug;11(4):497-507 497-507
DATE:	1998
AUTHOR OF ARTICLE:	Low LC; Wang Q
TITLE OF ARTICLE:	Gonadotropin independent precocious puberty.
ISSN:	[NOT AVAI
OTHER NOS/LETTERS:	Library reports holding volume or year 9508900 9777570
SOURCE:	PubMed
CALL NUMBER:	W1 JO828DR
REQUESTER INFO:	AB424
DELIVERY:	E-mail: probey@DIR.NIDCR.NIH.GOV
REPLY:	Mail:

Journal of Pediatric Endocrinology & Metabolism, 11, 497-507 (1998)

Gonadotropin Independent Precocious Puberty

Louis C.K. Low[1] and Qian Wang[2]

[1]*Department of Paediatrics, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong SAR*
[2]*Department of Paediatrics, The First Teaching Hospital, Beijing Medical University People's Republic of China*

INTRODUCTION

Precocious puberty is the onset of breast development before the age of eight years in girls and testicular enlargement before the age of nine years in boys. However the age cut-off used in the definition must be modified in the light of information on pubertal development in a particular population. Central precocious puberty (CPP) is defined as the early development of secondary sexual characteristics due to maturation of gonadal steroidogenesis and gametogenesis as a result of early maturation of the hypothalamic-pituitary-gonad axis. Precocious puberty leads to accelerated growth and skeletal maturation and compromised adult height /1/. Gonadotrophin releasing hormone (GnRH) analogue is the treatment of choice but improvement in final height is best in children who have been diagnosed and treated before six years of age /2/. Pseudoprecocious puberty is the early development of secondary sexual characteristics due to autonomous secretion of sex hormones as a result of primary disorders of the adrenal glands or gonads without evidence of gametogenesis or pubertal levels of gonadotrophins. Causes of pseudoprecocious puberty include congenital adrenal hyperplasia, human chorionic gonadotrophin (HCG) secreting tumors and tumors of the adrenal gland or ovary. In recent years, a third condition, gonadotrophin-independent precocious puberty (GIPP), has been described in patients with early maturation of gonadal steroidogenesis and gametogenesis without pubertal concentrations of pituitary secreted gonadotrophins /3/. This unique mode of precocious sexual development has been described in boys with familial or sporadic male-limited precocious puberty (FMPP or SMPP) /4/ and girls with the McCune-Albright syndrome /5/. This review focuses on what is currently known about the clinical presentation, mechanism of disease and treatment of gonadotrophin-independent precocious puberty.

Reprint address:
Professor Louis C.K. Low
Department of Paediatrics
Queen Mary Hospital
Pokfulam Road
Hong Kong SAR
People's Republic of China

FAMILIAL AND SPORADIC MALE-LIMITED PRECOCIOUS PUBERTY

Clinical features

Familial male-limited precocious puberty (FMPP) has been known for at least half a century and interest in the condition was revived in the 1980s /3,4,6-13/. The syndrome is characterized by sexual development with pubertal sex hormone concentrations and spermatogenesis in the absence of pituitary gonadotrophin secretion in a pubertal pattern. Although sporadic cases (SMPP) have been reported, the condition has only been described in males, extending to several generations of the family. The pattern of inheritance supports a sex-limited autosomal dominant transmission with greater than 90% penetrance, and female carriers are unaffected by early sexual development or endocrine abnormalities /7,8,9,12/. The male patients develop progressive secondary sexual characteristics with rapid physical growth and skeletal maturation often accompanied by sexually aggressive behavior within the first two to three years of life. The penis increases in size but testicular volume is increased to a size that is less than expected for the degree of sexual development /8-10,13/. Gonadotrophin-independent isosexual

precocity has been described in a boy with tuberous sclerosis /14/. Fertility is unaffected although evidence of premature gonadal failure may appear later in adulthood /9/.

Laboratory findings

The typical hormonal profile of patients with SMPP or FMPP consists of pubertal levels of testosterone in the presence of low basal luteinizing hormone (LH) and follicular stimulating hormone (FSH) concentrations with the lack of a pubertal rise in LH and FSH concentrations to GnRH stimulation /3,4,8-10,13,15/. A pulsatile pubertal pattern of LH and FSH secretion is distinctly absent throughout the day during the early phase of the disease /4,13,15/. The source of the elevated testosterone level is the testes and not the adrenal glands; bilateral adrenal vein sampling revealed no testosterone gradient /4,8/. Before the discovery of the molecular basis of FMPP (*vide infra*), the condition was thought to be due to an inherited intratesticular defect /4,8,9,16/, and bioactive LH had not been detected using a rat Leydig cell bioassay /3,8/. As serum concentrations of FSH in prepubertal children are much higher than that of LH, the detection of lower than normal levels of FSH using the newly established ultrasensitive immunofluorometric assay for gonadotrophins can be helpful in the diagnosis of GIPP and hypogonadotrophic hypogonadism /17/. Anti-Müllerian hormone (AMH) is produced by Sertoli cells from fetal life until puberty and an inverse relationship between AMH and testosterone had been demonstrated in both CPP and GIPP, suggesting that gonadotrophins are not directly implicated in repression of AMH synthesis at puberty but rather that the decrease in AMH production is the consequence of an androgen-mediated reversible chain of events leading to morphological and functional maturation of Sertoli cells /18/.

Testicular biopsies from patients with FMPP have revealed premature Leydig cell maturation or Leydig cell hyperplasia with variable degrees of active spermatogenesis especially adjacent to the Leydig cell aggregates /4,8-10,16/. Germ cells at all stages of spermatogenesis are present but there is evident disorganization of maturation and the spermatids exhibit a variety of structural abnormalities /16/. Although spermatogenesis has been generally thought to require FSH stimulation (which is low in FMPP), it may occur in response to high intratesticular concentrations of testosterone alone /19/. Sertoli cells are characterized by complex cytoplasmic differentiation compatible with premature differentiation of all major testicular cell types in FMPP.

The natural history of the condition can be divided into three stages: in childhood, there is gonadotrophin-independent Leydig cell hyperfunction; in adolescence and early adulthood pubertal gonadotrophin secretion is observed, both spontaneously and in response to GnRH; in later life, elevated LH and FSH levels are fond because of damage to the germinal tissue and decreasing Leydig cell function /9,11,15/. Despite exposure to pubertal levels of testosterone from early childhood and advanced skeletal maturation, the pattern and timing of hypothalamic maturation of GnRH-induced pulsatile gonadotrophin secretion appears normal for age in two longitudinally followed patients with GIPP /15/. In most patients with SMPP or FMPP, one can assume that the testes will come under pituitary regulation once the pubertal pattern of gonadotrophin secretion is established. The demonstration of autonomous gonadal steroid secretion in patients with GIPP treated with GnRH analogue after the onset of central puberty suggests that the potential for gonadal autonomy can persist into adulthood. In the Chinese family with FMPP that we have reported, low basal LH and FSH concentrations with no rise to GnRH stimulation was observed in a 35 year-old patient, indicating that gonadal autonomy with suppressed gonadotrophin secretion can occasionally persist into adulthood without establishing a pubertal pattern of pituitary gonadotrophin secretion /10/. The serum concentrations of adrenal androgens in patients with GIPP appear to increase in a chronological age-appropriate manner rather than in accordance with the degree of skeletal advancement /15/.

Molecular mechanism of disease

The human LH receptor is a member of the family of G-protein coupled receptors. The molecular defect of FMPP was first shown to be due to a dominant mutation in the LH receptor gene

that resulted in the production of a receptor that could undergo spontaneous activation in the absence of the agonist LH or HCG /20/. A single A to G base change that resulted in substitution of glycine for aspartate in position 578 in the sixth transmembrane helix of the LH receptor was found in affected individuals from eight different families /20/. COS-7 cells expressing the mutant LH receptor exhibited a markedly increased cyclic AMP production both basally and in response to HCG. Since then, many other mutations causing SMPP or FMPP have been reported in the literature with most of these mutations occurring between amino acid residues 542 and 581, encompassing transmembrane helix five and six and the third cytolasmic loop of the human LH receptor, suggesting that exon eleven of the LH receptor gene is the mutation hotspot (Table 1). These mutations may sometimes create a recognition site for a particular restriction endonuclease and restriction digest analysis can be used to investigate suspected cases of FMPP for a particular mutation (e.g. Msp I for D578G mutation, Rsa I for D564G mutation and Aci I for C581R mutation). The D578G mutation is the commonest mutation found in patients with MPP and the report of this mutation in other ethnic groups apart from Caucasians is against the possibility of a founder effect for this mutation. So far approximately 46% of SMPP and 77% of cases of FMPP result from the D578G

TABLE 1

Location of some known activating mutations of the human leuteinizing hormone receptor in familial male-limited precocious puberty

Amino Acid Change	Location	References
Met 398 to Thr	Transmembrane helix II	Yano [21], Kraaij [22]
Ile 542 to Leu	Transmembrane helix V	Laue [23]
Asp 564 to Gly	3rd cytoplasmic loop	Laue [23]
Ala 568 to Val	3rd cytoplasmic loop	Latronico [24]
Met 571 to Ile	Transmembrane helix VI	Laue [23], Kosugi [26]
Ala 572 to Val	Transmembrane helix VI	Yano [27]
Ile 575 to Leu	Transmembrane helix VI	Laue [25]
Thr 577 to Ile	Transmembrane helix VI	Laue [23] Kosugi [26]
Asp 578 to Tyr	Transmembrane helix VI	Laue [23]
Asp 578 to Gly	Transmembrane helix VI	Shenkar [20], Laue [23] Yano [28], Kawate [29] Kremer [30]
Cys 581 to Arg	Transmembrane helix VI	Laue [23]

mutation, and three other mutations, I542L, D568G and A572V, have been found in both forms of MPP /25/. Patients with non-Caucasian ethnic backgrounds appear to have a higher likelihood of having new mutations. Recent studies have provided evidence that it is the ability of the Asp 578 side chain to serve as a properly positioned hydrogen bond acceptor, rather than its negative charge, that is important for stabilizing the inactive state of the human LH receptor /31/. Both I542L and I575L involve substituting one non-polar residue with another non-polar residue of similar size. It seems likely that the change in position of the methyl group of these side chains modifies the relative positions of helices 5 and 6 and the position or accessibility of the third cytoplasmic loop, allowing the human LH receptor to assume a partially active conformation /25/. The surface expression of the constitutively activating I575L mutated LH receptor is diminished but agonist affinity is normal /25/. The relationship between the LH receptor mutation and the previously described testis-stimulating factor /32/ in FMPP is still not known and this factor is unlikely to be of importance in FMPP in light of more recent evidence.

The Gsα protein subunit couples more than twenty different receptors to stimulation of adenyl cyclase, and mutations in this gene can result in loss of function (pseudohypoparathyroidism type Ia) or gain in function as in McCune-Albright syndrome (*vide infra*) and endocrine tumors. Concurrent occurrence of pseudohypoparathyroidism type Ia and gonadotrophin independent precocious puberty has been reported in two boys who were found to have a unique mutation in the guanine nucleotide-binding protein subunit, Gsα /33/. The point mutation which results in an alanine to serine substitution in codon 366 of one Gsα allele is unique in the tissue specificity of its effect which is based in part on the instability of the mutant protein at core body temperature. This mutant protein has been shown to be stable and can constitutively increase intracellular cyclic AMP concentrations at 'testicular' temperature of 32°C but the mutant protein rapidly denatures, with loss of function at the usual core body temperature of 37°C /34/.

Treatment

Although direct effects of GnRH analogues on testicular steroidogenesis have been demonstrated, this effect does not appear to be important in humans. Continuous use of GnRH analogues effectively inhibits gonadotrophin secretion mainly through downregulation of pituitary receptors. In SMPP and FMPP, testosterone is secreted autonomously independent of pituitary gonadotrophins. It is therefore not unexpected that GnRH analogues, which have been effective in the treatment of GnRH-dependent central precocious puberty, have been found to be ineffective in the management of MPP /3,4,35/. Medroxyprogesterone acetate has been reported to be effective in suppressing the elevated plasma testosterone concentrations and accelerated growth in patients with MPP /4/. Medroxyprogesterone acetate inhibits testicular steroidogenesis at multiple enzyme steps including 17-hydroxylase, 17-20 lyase, 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase /36/. However, long term results of this form of treatment in MPP are not available.

Ketoconazole is an imidazole derivative and a broad spectrum antimycotic agent of low toxicity. Ketoconazole has also been shown to be a potent inhibitor of gonadal and adrenal steroidogenesis with a relatively selective effect on the C17-20 lyase step in steroid hydroxylation, but cholesterol side chain cleavage enzyme, 11-hydroxylase and 18 hydroxylase activities are also inhibited to a lesser extent /37/. Holland and co-workers were the first to report the effect of the use of this agent in the treatment of three patients with MPP /35/. Ketoconazole given in a dose of 200 mg twice daily led to a significant fall in serum testosterone concentrations and a rise in serum 17αhydroxyprogesterone within 24 hours and marked improvement in behavior with disappearance of penile erections and masturbatory activity within 48 hours of treatment. After starting treatment, there is a transient blunting of the cortisol reserve, but the cortisol response to ACTH and the diurnal rhythm is preserved with continued treatment /13,35/. The fall in serum testosterone is associated with a rise in serum 17α-hydroxyprogesterone but the concentrations of

andostenedione and dehydroepiandrosterone sulfate remain unchanged. The dose of ketoconazole may need to be increased to 200 mg every 8 hours. An 'escape phenomenon' is commonly seen in patients with continued therapy resulting in a progressive rise in serum testosterone and a pubertal gonadotrophin response to GnRH. Satisfactory control can once again be achieved when treatment with a GnRH analogue is added to ketoconazole therapy /38/. Side effects of treatment include gastrointestinal upset, headache and irritability. At high doses adrenal insufficiency may occur. About 10% of patients have transient hepatic dysfunction but the incidence of true hepatic damage is low (0.1% to 1%) /37/. Long term use of the combination of GnRH analogue and ketoconazole treatment appears to be effective and safe in 11 patients /13/.

As an alternative approach to the treatment of MPP, blockade of androgen with spironolactone may reverse the signs of puberty in boys. Persistent estrogen synthesis during spironolactone treatment may maintain rapid growth and skeletal maturation and gynecomastia /39/. Testolactone, a competitive aromatase inhibitor, will theoretically be required in addition. Neither spironolactone nor testolactone when given alone can achieve satisfactory control of MPP. Spironolactone is started at 2 mg/kg/day and the dose is increased to 4 mg/kg/day and 5.7 mg/kg/day after 2 and 4 weeks respectively. The starting dose of testolactone is 20 mg/kg/day (in four divided doses) increasing by 10 mg/kg/day every two weeks to 40 mg/kg/day. The combination of these two drugs restored the growth velocity and skeletal maturation to normal prepubertal rates /39/. As the elevated serum testosterone concentrations do not change with spironolactone treatment and testolactone or its metabolite interferes with the estradiol assay, measurements of serum testosterone and estradiol are unhelpful in monitoring treatment. Assessment of satisfactory control depends on control of secondary sexual characteristics and return of growth velocity and skeletal maturation to a prepubertal level. With longer term treatment, most children with MPP exhibit a pubertal rise in gonadotrophin secretion. The rise in gonadotrophin levels during central activation of hypothalamic GnRH secretion in boys with MPP causes an 'escape' from the combined effect of spironolactone and testolactone. The addition of GnRH analogue to combined therapy appears to restore control of puberty /40/. Proof that any form of treatment of MPP can improve final adult height is still awaited.

McCUNE-ALBRIGHT SYNDROME

Clinical features

McCune-Albright syndrome (MAS) is a sporadic disorder characterized by GIPP, café-au-lait pigmented macules which have an irregular (coast of Maine) border, and polyostotic fibrous dysplasia, first described by McCune /41/ and Albright *et al.* /42/. However, pigmentation may be absent and not all the patients with polyostotic fibrous dysplasia and pigmentation have precocious puberty. The disease is sporadic and occurs in most ethnic groups, affecting females more commonly than males. The apparent predominance of females in McCune-Albright syndrome may reflect a gender difference in the recognition and diagnosis due to the high frequency of sexual precocity in girls.

The bone involvement is multifocal in the majority of the cases of MAS with the limb bones most commonly affected, resulting in deformity and occasionally fractures. The bony abnormalities of MAS may not be apparent on plain radiographs early in life and a technetium bone scan may be a more sensitive tool in demonstrating fibrous bone dysplasia. The distortion of facial features (leontiasis ossia) frequently results from fibrous dysplasia of the facial bones which may also cause compression of the optic or acoustic nerves, leading to visual or hearing impairment /43/. Precocious puberty in girls with MAS has been attributed in some cases to early activation of the hypothalamic-pituitary-gonadal axis (CPP) but more commonly to cyclic estrogen secretion by autonomously functioning ovarian cysts in patients who are found to have suppressed gonadotrophin concentrations /44/. There is rapid progression of breast enlargement and pigmentation of the nipples together with growth acceleration concurrent with follicular cyst development, and uterine bleeding will occur with involution of the cyst. When the interval between cyst formation is sufficiently long to permit some

regression of the secondary sexual characteristics, then the clinical picture can be one of waxing and waning pubertal development. High circulating estrogen levels can induce early growth of genital hair and apocrine sweat gland activity despite prepubertal concentrations of adrenal androgens, because the high estrogen level can increase the sensitivity of androgen-responsive end organs /45/. In a patient with MAS, granulosa cells obtained from a cyst at laparotomy and cultured *in vitro* were found to produce much higher levels of estradiol as compared to granulosa cells obtained from normal individuals /46/. A new incomplete form of MAS in a patient with GIPP, café-au-lait pigmentation and scalp alopecia due to cutaneous fibrous dysplasia has recently been described /47/. GIPP has also been described in a female patient with Leri-Weill dyschondrosteosis /48/.

MAS is a multisystem disease and hyperthyroidism, acromegaly or gigantism due to growth hormone excess, hyperprolactinemia, Cushing's syndrome and osteopenia with hypophosphatemia are commonly encountered in these patients. Growth hormone excess in MAS occurs with equal frequency in males and females, but radiographic evidence of a pituitary tumor has only been reported in 40% of cases /49/. Hyperprolactinemia is found in 80-90% of MAS patients with growth hormone excess as oppose to 30-40% in other cases of acromegaly. Mammosomatotroph hyperplasia has been reported in such patients /50/. The responses to growth hormone releasing hormone (GHRH) and octreotide suggest that the pituitary function in such patients is not totally autonomous, and elevated plasma levels of GHRH have not been found /49/. In children with McCune-Albright syndrome without acromegaly, the 24-hour growth hormone profile and serum insulin-like growth factor I (IGF-I) concentrations are no different from normal pubertal children /51/. Similarly elevated levels of thyroid stimulating hormone, gonadotrophins and adrenocortical stimulating hormone have not been found to be the cause of hyperthyroidism /43/, precocious puberty and Cushing's syndrome /52/ in patients with MAS. Hypophosphatemia and osteopenia have been found in 20% of patients /43/. Serum calcium, parathyroid hormone and vitamin D concentrations have all been normal.

Laboratory findings

Polyostotic fibrous dysplasia of bone can be demonstrated by radiological skeletal survey or technetium bone scan. GIPP is confirmed by a prepubertal pattern of spontaneous gonadotropin secretion and a lack of rise of gonadotrophin concentration to GnRH stimulation in the presence of a pubertal level of estradiol /44/. The lack of any clinical or hormonal response to GnRH analogue is further evidence that the precocious puberty in MAS is not dependent on pituitary gonadotrophins /53/. Rarely, a patient with MAS may present with CPP and such patients will usually respond to GnRH analogue /44,53/. Occasionally precocious puberty due to autonomous ovarian hyperfunction can be followed by gonadotrophin dependent puberty in MAS patients /54,55/.

Ultrasonographic examination (USG) of the pelvis is crucial in the assessment of precocious puberty in MAS. The degree of asymmetry between the right and left ovaries has been found to be significantly greater in girls with MAS as compared to girls with CPP. Asymmetry is due to the presence of large solitary cysts in the larger of the two ovaries /56/. Serial USG is useful in the monitoring of progress of the disease and also the response to treatment. High circulating levels of estradiol correlate well with cyst size, and involution of the cyst will result in a fall in serum estradiol and uterine bleeding /56,57/. We have not been able to demonstrate any FSH bioactivity using a rat granulosa cell assay /58/ in children with recurrent ovarian cysts with or without features of MAS /57/. On the contrary, increased FSH bioactivity was reported in two out of six children with MAS by Foster and coworkers but the activity did not vary with ovarian cyst size /56/. It is important to realize that there are quite a number of reports in the literature of patients with GIPP due to recurrent ovarian cyst formation without the features of MAS /57,59-62/. It has been proposed that the underlying defect of MAS may be expressed in the ovaries but not in the skin or bones of these patients /60/. In addition one should monitor for the development of other endocrinopathies and non-endocrine abnorm-

alities, including hypophosphatemia, chronic liver dysfunction, intestinal adenomatous polyps, thymic hyperplasia and cardiopulmonary abnormality.

Molecular mechanism of disease

The explanation for the autonomous function of multiple endocrine glands in patients with MAS is the overactivity of the cyclic AMP signaling pathway. The G-proteins involved in signal transduction are heterotrimers consisting of α, β and γ subunits, each of which are encoded by separate genes /63/. Inactive stimulatory G-protein (Gs) is normally activated by interaction with a hormone-bound receptor resulting in exchange of GTP for GDP and dissociation of the α subunit. In the case of Gs, the GTP-bound α subunit interacts with and stimulates adenylate cyclase and specific ion channels. The intrinsic GTPase activity of the α subunit inactivates the G-protein /64/. Certain mutations in the Gsα gene can result in inhibition of GTPase activity of Gs, prolonging the action of the active protein in the absence of stimulatory hormone. Such mutations, also known as *gsp* mutations, have been described in endocrine tumors. Somatic Gsα gene mutations in codon 201 (arginine to either cysteine or histidine) and codon 227 (glutamine to histidine) have been reported in GH-secreting pituitary tumors or thyroid adenomas. Mutations in the Arg^{179} codon of inhibitory G-protein-2 α subunit ($G\alpha i_2$) have been detected in adrenal and ovarian tumors /65/. As autonomous functioning of multiple endocrine glands is common in MAS, it has been hypothesized that early somatic mutations of the Gsα gene may be responsible for the disease. Two somatic activating mutations within exon 8 of the Gsα gene (arginine 201 to cysteine and arginine 201 to histidine) were detected in different tissues of patients with MAS /66,67/. The proportion of cells affected by these mutations varied from tissue to tissue in different patients with MAS /66,68/. As these mutations are found in tissues derived from the ectoderm, mesoderm and endoderm, the mutational event must therefore take place before the development of the trilaminar disk early in embryogenesis. Gsα mutations have been detected in tissues (pancreas, blood) with no clinical abnormalities, and one possible explanation is that there is low expression of the mutant gene as messenger RNA or protein in these tissues. The development of cystic ovaries and precocious sexual development in MAS has now been shown to be due to the gonadotrophin-independent maturation of primordial follicles harboring these *gsp* mutations. Patients with GIPP due to recurrent ovarian cyst formation without other features of MAS may also have such mutations limited to the ovaries but proof of such an occurrence is still awaited /60/.

In two girls with precocious puberty due to recurrent autonomous ovarian cyst formation without features of MAS, the basal 17αhydroxyprogesterone (17αOHP) levels were reported to be normal, but the exaggerated 17αOHP response to ACTH and the failure of suppression of the 17αOHP levels with dexamethasone suggested an abnormality of adrenal androgen secretion in these two patients /61/. In addition these girls also had increased levels of dehydroepiandrosterone sulfate, 16-hydroxydehydroepiandrosterone sulfate and another unidentified steroid sulfate in their serum as well as in the cyst fluid. It was proposed that increased steroid production by the adrenal gland stimulated the development of ovarian cysts which would in turn convert the adrenal steroids to estrogen, leading to increasing cyst size and estrogen production. However, the importance of this observation in relation to the recently elucidated molecular defect remains to be established.

Treatment

As precocious puberty in patients with MAS is usually gonadotrophin independent, GnRH analogue therapy has not been found to be useful /53,57/. Cyproterone acetate, which is a steroidal antiandrogen, has been used to treat such patients (occasionally together with a GnRH analogue) usually in a dose ranging from 50 to 150 mg/m^2/day. The drug may be effective in controlling the progress of the secondary sexual characteristics but treatment does not appear to improve final adult height /69,70/. Information on treatment with medroxyprogesterone acetate is limited and its action depends on its local anti-estrogen properties

rather than its inhibitory effect on gonadotropin secretion. The effect on final adult height is similar to cyproterone acetate.

Testolactone is an aromatase inhibitor and exerts its anti-estrogen effects through inhibition of the enzymatic conversion of androstenedione to estrone and testosterone to estradiol. The first reports of successful use of testolactone in MAS appeared in 1985 and 1987 /71,72/. In a more recent report, testolactone in a dose of 40 mg/kg/day was used in the treatment of 12 children with MAS for periods of 0.5 to 5 years; seven children received treatment for more than 3 years /73,74/. Treatment resulted in a significant fall in serum estradiol concentrations, menstrual episodes, ovarian volume and growth velocity. However the serum estradiol did not suppress to prepubertal levels and infrequent menses still occurred. Recurrence of ovarian cyst was observed in two of the seven children at the end of 3 years of treatment. In three of the girls with skeletal age more than 12 years, the gonadotrophin response to GnRH indicated CPP after 1-4 years of treatment. Such patients would likely benefit from the addition of a GnRH analogue to the treatment regimen. No significant improvement in predicted adult height occurred after 3 years of treatment /74/; final height data from treated patients are awaited. Most patients experienced problems with compliance, and side effects of treatment included transient abdominal pain, headache, diarrhea and abnormal liver enzymes.

In a report of the long-term follow up of 15 MAS patients, four female patients reached a final height which was not different from the mean of normal females /43/. The patients developed regular menses and two had children. However, persistence of autonomous ovarian function and irregular menses into adult life has been reported. Surgery has sometimes been used to control pubertal development /45,69/, but it should be discouraged as recurrence is likely. In patients with other endocrinopathies and non-endocrine abnormalities, these problems should receive appropriate attention in terms of investigations and treatment. Of special interest are the patients with GH excess; pituitary surgery should only be undertaken after careful consideration as there is a high frequency of vascular parasellar bony involvement by fibrous dysplasia /49/.

SUMMARY

Clinicians should now be fully aware of this intriguing condition of GIPP. The condition is characterized by pubertal sex steroid concentrations and gametogenesis in the presence of prepubertal or suppressed gonadotrophins. In patients with MPP especially without a family history, one should exclude the possibility of pseudoprecocious puberty due to premature production of sex steroids without pituitary gonadotrophins resulting from a primary disorder of the gonad or adrenal gland or to autonomous secretion of gonadotrophin by a tumor. Similarly in patients with recurrent ovarian cyst formation, persistence of the cysts especially with a significant solid component beyond three months should alert a clinician to the possibility of juvenile granulosa cell tumor of the ovary /75/. After confirmation of the diagnosis appropriate treatment should be instituted.

ACKNOWLEDGEMENTS

The authors would like to thank Ms Jessica Cheng for her help with the manuscript.

REFERENCES

1. Schoevaart CE, Drop SLS, Otten BJ, Slijpen FME, Degenhart HJ. Growth analysis up to final height and psychosocial adjustment of treated and untreated patients with precocious puberty. Horm Res 1990; 34: 197-203.
2. Kletter GB, Kelch RP. Effects of gonadotropin-releasing hormone analogue therapy on adult stature in precocious puberty. J Clin Endocrinol Metab 1994; 79: 331-334.
3. Wierman ME, Beardworth DE, Mansfield MJ, Badger TM, Crawford JD, Crigler JF Jr, Bode HH, Loughlin JS, Kushner DC, Scully RE, Hoffman WH, Crowley WF. Puberty without gonadotropins. A unique mechanism of sexual development. N Engl J Med 1985; 315: 65-72.
4. Rosenthal SM, Grumbach MM, Kaplan SL. Gonadotropin-independent precocious puberty (familial testotoxicosis): effects of a potent luteinizing hormone-releasing factor agonist and medroxyprogesterone

acetate therapy in four cases. J Clin Endocrinol Metab 1983; 57: 571-579.
5. Foster CM, Ross JL, Shawker T, Pescovitz OH, Loriaux DL, Cutler GB Jr, Comite F. Absence of pubertal gonadotropin secretion in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 1984; 58: 1161-1165.
6. Mortimer EA. Family constitutional precocious puberty in a boy three years of age. Pediatrics 1954; 13: 174-177.
7. Beas F, Zurbrugg RP, Leibow SG, Patton RG, Gardner LI. Familial male sexual precocity: report of the eleventh kindred found, with observations on blood group linkage and urinary C_{19}-steroid excretion. J Clin Endcrinol Metab 1962; 22: 1095-1102.
8. Schedewie HK, Reiter EO, Beitins IZ, Seyed S, Wooten VD, Jimenez JF, Aiman EJ, DeVane GW, Redman JF, Elders MJ. Testicular Leydig cell hyperplasia as a cause of familial sexual precocity. J Clin Endocrinol Metab 1981; 52: 271-278.
9. Egli CA, Rosenthal SM, Grumbach MM, Montalvo JM, Gondos B. Pituitary gonadotropin-independent male-limited autosomal dominant sexual precocity in nine generations: familial testotoxicosis. J Pediatr 1985; 106: 33-40.
10. Lim YJ, Low LCK. Familial testotoxicosis in a Chinese family. Eur J Pediatr 1994; 153: 241-244.
11. Reiter EO, Brown RS, Longcoke C, Beitins IZ. Male-limited familial precocious puberty in three generations: apparent Leydig-cell autonomy and elevated glycoprotein hormone alpha subunit. N Engl J Med 1984; 311: 515-519.
12. Pike AW, Klein JL, Gotlin RW, Fennessey PV. The role of steroid metabolic profiling as an aid in the diagnosis of familial precocious puberty, a subgroup of true precocious puberty. J Inherit Metab Dis 1986; 9: 147-155.
13. Holland FJ. Gondotropin-independent precocious puberty. Endocrinol Metab Clin North Am 1991; 20: 191-210.
14. Root AW, Zamanillo J, Duckett G, Sweetland M. Gonadotropin-independent isosexual precocity in a boy with tuberous sclerosis: effect of ketoconazole. J Pediatr 1986; 109: 1012-1015.
15. Boepple PA, Frisch LS, Wierman ME, Hoffman WH, Crowley WF Jr. The natural history of autonomous gonadal fucntion, adrenarche, and central puberty in gonadotropin independent precocious puberty. J Clin Endocrinol Metab 1992; 75: 1550-1555.
16. Gondos B, Egli CA, Rosenthal SM, Grumbach MM. Testicular changes in gonadotropin-independent familial male sexual precocity. Arch Pathol Lab Med 1985; 109: 990-995.
17. Apter D. Ultrasensitive new immunoassays for gonadotropins in the evaluation of puberty. Curr Opin Pediatr 1993; 5: 481-487.
18. Rey R, Lordereau-Richard I, Carel JC, Barbet P, Cate RL, Roger M, Chaussin JL, Josso N. Anti-mullerian hormone and testosterone serum levels are inversely proportional during normal and precocious pubertal development. J Clin Endocrinol Metab 1993; 77: 1220-1226.
19. Steinberger E, Root A, Ficher M, Smith KD. The role of androgens in the initiation of spermatogenesis in man. J Clin Endocrinol Metab 1973; 37: 746-751.
20. Shenkar A, Laue L, Kosugi S, Merendino JJ Jr, Minegishi T, Cutler GB Jr. A constitutively activating mutation of the luteinizing hormone receptor in familial male precocious puberty. Nature 1993; 365: 652-654.
21. Yano, Kohn LD, Saji M, Kataoka N, Okuno A, Cutler GB Jr. A case of male-limited precocious puberty caused by a point mutation in the second transmembrane domain of the luteinizing hormone choriogonadotropin receptor gene. Biochem Biophys Res Comm 1996; 220: 1036-1042.
22. Kraaij R, Post M, Kremer H, Milgrom E, Epping W, Brunner HG, Grootegoed JA, Themmen AP. A missense mutation in the second transmembrane segment of the luteinizing hormone receptor causes familial male-limited precocious puberty. J Clin Endocrinol Metab 1995; 80: 3168-3172.
23. Laue L, Chan WY, Hsueh AJ, Kudo M, Hsu SY, Wu SM, Blomberg L, Cutler GB Jr. Genetic heterogeneity of constitutively activating mutations of the human luteinizing hormone receptor in familial male-limited precocious puberty. Proc Natl Acad Sci USA 1995; 92: 1906-1910.
24. Latronico AC, Anasti J, Arnhold IJ, Mendonca BB, Domenice S, Albano MC, Zachman K, Wajchenberg BL, Tsigos C. A novel mutation of the luteinizing hormone receptor gene causing male gonadotropin-independent precocious puberty. J Clin Endocrinol Metab 1995; 80: 2490-2494.
25. Laue L, Wu SM, Kudo M, Hsueh AJW, Cutler GB Jr, Jelly DH, Diamond FB, Chan WY. Heterogeneity of activating mutations of the human luteinizing hormone receptor in male-limited precocious puberty. Biochem Mol Med 1996; 58: 192-196.
26. Kosugi S, Van Dop C, Geffner ME, Rabl W, Carel JC, Chaussain JL, Mori T, Merendino Jr JJ, Shenkar A. Characterization of heterogeneous mutations causing constitutive activation of the luteinizing hormone receptor in familial male precocious puberty. Hum Mol Genet 1995; 4: 183-188.
27. Yano K, Saji M, Hidaka A, Moriya N, Okuno A, Kohn LD, Cutler Jr GB. A new constitutively activating point mutation in the luteinizing hormone/choriogonadotropin receptor gene in cases of male-limited precocious puberty. J Clin Endocrinol Metab 1995; 80: 1162-1168.
28. Yano K, Hidaka A, Saji M, Polymeropoulos MH, Okuno A, Kohn LD, Cutler GB Jr. A sporadic case of male-limited precocious puberty has the same constit-

utively activating point mutation in luteinizing hormone/choriogonadotropin receptor gene as familial cases. J Clin Endocrinol Metab 1994; 79: 1818-1823.
29. Kawate N, Kletter GB, Wilson BE, Netzloff ML, Menon KM. Identification of constitutively activating mutation of the luteinizing hormone receptor in a family with male limited gonadotropin independent precocious puberty (testotoxicosis). J Med Genet 1995; 32: 553-554.
30. Kremer H, Mariman E, Otten BJ, Moll GW Jr, Stoelinga GB, Wit JM, Jansen M, Drop SL, Faas B, Ropers HH, Brunner HG. Cosegregation of missense mutations of the luteinizing hormone receptor gene with familial male-limited precocious puberty. Hum Mol Genet 1993; 2: 1779-1783.
31. Kosugi S, Mori T, Shenkar A. The role of Asp 578 in maintaining the inactive conformation of human lutropin/choriogonadotropin receptor. J Biol Chem 1996; 271: 31813-31817.
32. Manasco PK, Girtow ME, Diggs RL, Doppman JL, Feuillan PP, Barnes KM, Cutler GB Jr, Loriaux DL, Albertson BD. A novel testis-stimulating factor in familial male precocious puberty. N Engl J Med 1991; 324: 227-231.
33. Nakamoto JM, Zimmerman D, Jones EA, Loke KY, Siddiq K, Donlan MA, Brickman AS, Van Dop C. Concurrent hormone resistance (pseudohypoparathyroidism type Ia) and hormone independence (testotoxicosis) caused by a unique mutation in the GαS gene. Biochem Mol Med 1996; 58: 18-24.
34. Iiri T, Herzmark P, Nakamoto JM, Van Dop C, Bourne HR. Rapid GDP release from Gsα in patients with gain and loss of endocrine function. Nature 1994; 371: 164-168.
35. Holland FJ, Fishman L, Bailey JD, Fazekas ATA. Ketoconazole in the management of precocious puberty not responsive to LHRH-analogue therapy. N Engl J Med 1985; 313: 1023-1028.
36. Barbieri RL, Ryan KT. Direct effects of medroxyprogesterone acetate (MPA) and megestrol acetate (MGA) on rat testicular steroidogenesis. Acta Endocrinol (Copenh) 1980; 94: 419-425.
37. Sonino N. The use of ketoconazole as an inhibitor of steroid production. N Engl J Med 1987; 317: 812-817.
38. Holland FJ, Kirsch SE, Selby R. Gonadotropin independent prococious puberty ('testotoxicosis'): influenze of maturational status on response to ketoconazole. J Clin Endocrinol Metab 1987; 64: 328-333
39. Laue L, Kenisberg D, Pescovitz OH, Hench KD, Barnes KM, Loriaux DL, Cutler GB Jr. Treatment of familial male precocious puberty with spironolactone and testolactone. N Engl J Med 1989; 320: 496-502.
40. Laue L, Jones J, Barnes KM, Gutler GB Jr. Treatment of familial male precocious puberty with spironolactone, testolactone and desorelin. J Clin Endocrinol Metab 1993; 76: 151-155.
41. McCune DJ. Osteitis fibrosa cystica: the case of a nine year old girl who also exhibits precocious puberty, multiple pigmentation of skin and hyperthyroidism. Am J Dis Child 1936; 52: 743-747.
42. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females. N Engl J Med 1937; 26: 726-746.
43. Lee PA, Van Dop C, Migeon CJ. McCune-Albright syndrome. Long-term follow-up. JAMA 1986; 256: 2980-2984.
44. Foster CM, Ross JL, Shawker T, Pescovitz OH, Loriaux DL, Cutler GB Jr, Comite F. Absence of pubertal gonadotropins secretion in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 1984; 58: 1161-1165.
45. Case records of the Massachusetts General Hospital. N Engl J Med 1989; 321: 1463-1471.
46. Manna C, Epifano O, Riminucci M, Baschieri L, Stephanini M, Canipari R. In vitro production of oestradiol by ovarian granulosa cells in a case of McCune-Albright syndrome. J Endocrinol Invest 1991; 14: 311-315.
47. Schwartz RA, Spicer MS, Leevy CB, Ticker JB, Lambert WC. Cutaneous fibrous dysplasia: an incomplete form of McCune-Albright syndrome. Dermatology 1996; 192: 258-261.
48. Patel L, Clayton PE, Super M, Price DA. Gonadotrophin-independent precocious puberty and dyschondrosteosis. J Pediatr Endocrinol 1994; 7: 265-267.
49. Cutler L, Jackson JA, Saeed uz-Zafar M, Levisky LL, Mellinger RC, Frohman LA. Hypersecretion of growth hormone and prolactin in McCune-Albright syndrome. J Clin Endocrinol Metab 1989; 68: 1148-1154.
50. Kovacs K, Horvath E, Thorner MO, Rogol AD. Mammosomatotroph hyperplasia associated with acromegaly and hyperprolactinemia in a patient with McCune-Albright syndrome. Virchows Arch [Pathol Anat] 1984: 403: 77-86.
51. Feuillan PP, Jones J, Ross JL. Growth hormone hypersecretion in a girl with McCune-Albright syndrome: Comparison with controls and response to a dose of long-acting somatostatin analog. J Clin Endocrinol Metab 1995; 80: 1357-1360.
52. Danon M, Robboy SJ, Kim S, Scully R, Crawford JD. Cushing syndrome, sexual precocity and polyostotic fibrous dysplasia (Albright syndrome) in infancy. J Pediatr 1975; 87: 917-921.
53. Foster CM, Comite F, Pescovitz OH, Ross JL, Loriaux DL, Cutler GB Jr. Variable response to a long-acting agonist of luteinizing hormone-releasing hormone in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 1984; 59: 801-805.
54. Kaufman PR, Costin G, Reid BS. Autonomous ovarian hyperfunction followed by gonadotrophin-dependent

puberty in McCune-Albright syndrome. Clin Endocrinol 1986; 24: 239-242.
55. Pasquino AM, Tebaldi L, Cives C, Maciocci M, Boscherini B. Precocious puberty in the McCune-Albright syndrome. Progression from gonadotrophin-independent to gonadotrophin-dependent puberty in a girl. Acta Paediatr Scand 1987; 76: 841-843.
56. Foster CM, Feuillan P, Padmanabhan V, Pescovitz OH, Beitins IZ, Comite, Shawker TH, Loriaux DL, Cutler GB Jr. Ovarian function in girls with McCune-Albright syndrome. Pediatr Res 1986; 20: 859-863.
57. Low LCK, Wang C, Leung A, Leong LY. Undetectable levels of serum FSH immunoactivity and bioactivity in girls with sexual precocity due to ovarian cysts. Acta Paediatr 1994; 83: 623-626.
58. Wang C, Zhong CQ, Leung A, Low LCK. Serum bioactive follicle-stimulating hormone levels in girls with precocious sexual development. J Clin Endocrinol Metab 1990; 70: 615-619.
59. Stokvis-Brantsma WH, van Weissenbruch MM, Wit JM, Schoemaker J, Drexhage HA. Sexual precocity induced by ovarian follicular cysts. Is autoimmunity involved? Clin Endocrinol 1990; 32: 603-612.
60. Feuillan PP, Jones J, Oerter KE, Manasco PK, Cutler GB Jr. Luteinizing hormone-releasing hormone (LHRH)-independent precocious puberty unresponsive to LHRH agonist therapy in two girls lacking features of the McCune-Albright syndrome. J Clin Endocrinol Metab 1991; 73: 1370-1373.
61. Chasalow FI, Granoff AB, Tse TF, Blethen SL. Adrenal steroid secretion in girls with pseudoprecocious puberty due to autonomous ovarian cysts. J Clin Endocrinol Metab 1986; 63: 828-834.
62. Richards GE, Kaplan SL, Grumbach MM. Sexual precocity caused by ovarian follicular cysts: Spontaneous regression and recurrence with prepubertal gonadotropin levels. Pediatr Res 1977; 11: 431A.
63. Simon MI, Strathmann MP, Gautam N. Diversity of G proteins in signal transduction. Science 1991; 252: 802-808.
64. Bourne HR, Sanders DA, McCormick F. The GTPase superfamily: a conserved switch for diverse cell function. Nature 1990; 348: 125-132.
65. Lyons J, Landis CA, Harsh G, Vallar L, Grunewald K, Feichtinger H, Duh QY, Clark OH, Kawasaki E, Bourne HR, McCormick F. Two G protein oncogenes in human endocrine tumours. Science 1990; 249: 655-659.
66. Weinstein LS, Shenkar A, Gejman SV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 1991; 325: 1688-1695.
67. Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. Proc Natl Acad Sci USA 1992; 89: 5152-5156.
68. Endo M, Yamada Y, Matsura N, Niikawa N. Monzygotic twins discordant for the major signs of McCune-Albright syndrome. Am J Med Genet 1991; 41: 216-220.
69. Sorgo W, Kirally E, Homoki J, Heinze E, Teller WM, Bierich JR, Moeller H, Ranke MB, Butenandt O, Knorr D. The effects of cyproterone acetate in statural growth in children with precocious puberty. Acta Endocrinol Copenh 1987; 115: 44-56.
70. Carani C, Pachioni C, Baldini A, Zini D. Effects of cyproterone acetate, LHRH agonist and ovarian surgery in McCune-Albright syndrome with precocious puberty and galactorrhoea. J Endocrinol Invest 1988; 11: 419-423.
71. Foster CM, Pescovitz OH, Comite F, Feuillan P, Shawker T, Loriaux DL, Cutler GB Jr. Testolactone treatment of precocious puberty in McCune-Albright syndrome. Acta Endocrinol Copenh 1985; 109; 254-257.
72. Hauffa BP, Havers W, Stolecke H. Short-term effects of testolactone compared to other treatment modalities on longitudinal growth and ovarian activity in a girl with McCune-Albright syndrome. Helv Paediatr Acta 1987; 42: 471-480.
73. Feuillan PP, Foster CM, Pescovitz OH, Hench KD, Shawker T, Dwyer A, Malley JD, Barnes K, Loriaux DL, Cutler GB Jr. Treatment of precocious puberty in the McCune-Albright syndrome with the aromatase inhibitor testolactone. N Engl J Med 1986; 315: 1115-1119.
74. Feuillan PP, Jones J, Cutler GB Jr. Long-term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. J Clin Endocrinol Metab 1993; 77: 647-651.
75. Young RH, Dickersin GR, Scully RE. Juvenile granulosa cell tumor of the ovary. A clinicopathological analysis of 125 cases. Am J Surg Pathol 1984; 8: 575-596.